Partners in Science:

The Umbrella CRADA Streamlines Collaborations Between CCR and Industry

Researchers across CCR are studying the molecular mechanisms that underlie multiple diseases. Some take as their starting point the mutations that confer genetic susceptibility in familial cancers; others may start with animal models. But the goal is the same–to prevent and treat disease by manipulating dysfunctional molecular networks. Although there are many research tools available to tease apart these networks, ultimately what is required are drugs that can be administered safely and effectively to patients. The pharmaceutical industry has a number of compounds in pipelines that are usually narrowly focused on a few target diseases. CCR has the expertise to test these compounds—alone or in combination—in robust preclinical models, as well as in the clinic. The advantages of collaboration are clear, but historically it has been difficult for individual investigators to broker the necessary negotiations with individual companies. CCR's Office of Policy and Intellectual Property, led by Eric Hale, J.D., M.B.A., has recently entered into a new kind of agreement between CCR and AstraZeneca—an Umbrella CRADA—which has made this type of collaboration much easier.

(Photo: R. Barr)

Eric Hale, J.D., M.B.A. *(left)*, Grace Chao Yeh, Ph.D. *(center)*, and Li Guo, Ph.D. *(right)*, work in CCR's Office of Policy and Intellectual Property to adapt the Cooperative Research and Development Agreements (CRADAs) to benefit both the scientists at CCR and the companies that wish to collaborate with them.

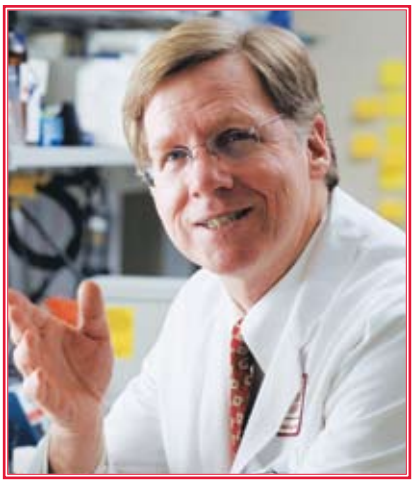
Beverly Mock, Ph.D., Head of the Cancer Genetics Section of CCR's Laboratory of Cancer Biology and Genetics, is eager to test AstraZeneca's inhibitor of mTOR (mammalian Target of rapamycin) in her xenograft models of multiple myeloma. In her research, she and her colleagues have recently demonstrated that a combination of the mTOR inhibitor rapamycin and an inhibitor of histone deacetylase (HDAC) has a powerful antitumor effect. Their analysis of the signaling pathways involved leads them to believe that the AstraZeneca compound may produce a similar effect, and validation of this hypothesis will be additional evidence towards their model of abnormal signaling at the root of plasma cell tumors.

W. Marston Linehan, M.D., Chief of CCR's Urologic Oncology Branch, has already started using the AstraZeneca mTOR inhibitor in cell lines derived from a patient with Birt-Hogg-Dube (BHD) syndrome and has seen very promising results. The inhibitor could be taken into clinical trials if the drug reaches that stage of development. Independently, their research on the mechanisms of action in this hereditary kidney cancer has converged with the targets of AstraZeneca's drug in what Linehan hopes will be "a perfect match."

Through the Umbrella CRADA mechanism, CCR is now offering

(Photo: B. Branson)

Beverly Mock, Ph.D.



(Photo: R. Baer)

W. Marston Linehan, M.D.

companies the means to study the biological activities of compounds in the context of highly developed scientific and clinical research programs that confer the ability to ask questions that companies are not themselves equipped to study. "These signals are important in validating internally that what you have spent a lot of time and treasure developing actually has biological activity," explained Gregory Curt, M.D., AstraZeneca's U.S. Medical Science Lead.

It is not by chance that one of the most successful Umbrella CRADAs was negotiated between CCR and AstraZeneca. Curt, the man responsible for establishing the collaboration on behalf of the company, spent 22 years at NCI, including 12 years as Clinical Director of CCR. "I know the program intimately and recognize what it can do uniquely," explained Curt. "We [pharmaceutical companies] tend to look at drugs from the prism of drugs. NCI tends to look at drugs from the prism of diseases. There is a real partnership to be gained there."

Why an Umbrella CRADA?

A standard CRADA is a written agreement between a federal research organization and one or more federal or non-federal parties (collaborators) to work together as partners on a research project of mutual interest (see "CRADA History"). Until recently, CRADAs at NCI have all been handled on an individual basis. An investigator conceives an idea (which he or she would discuss with a company representative), develops a research plan, and works with NCI's Technology Transfer Center to develop the proposed agreement. This agreement is subject to review by an NIH-wide CRADA subcommittee to ensure that issues such as fair access and conflicts of interest are handled appropriately. This process can take up to a year and can create inconsistencies even across different CRADAs with the same company.

"I am not a lawyer, nor a technology transfer guru," explained Linehan, although he nonetheless sometimes found himself sitting down with companies to allay misplaced fears of government obstacles to collaboration with industry. "Once you have that out of the way, it's fine," he added, noting that when all you want to do is make progress scientifically, there are far fewer barriers than most companies imagine. "But the process takes a long time, and if you are trying to do this for each company, it slows you down and slows you down, and you just give up after a while."

To streamline the CRADA process for all parties concerned, Hale and his colleagues Grace Yeh, Ph.D., and Li Guo have taken it to a new level. A first of its kind for the federal government or industry, the Umbrella CRADA is an agreement designed to permit large-scale collective partnering with industry. "These Umbrella CRADAs represent an attractive new way for CCR to collaborate with industry," explained Hale. Instead of a single laboratory negotiating the specific use of a single compound, the CCR Director's Office obtains access to an entire pipeline of compounds for more broadly stated purposes. Under the Umbrella CRADA, individual projects are submitted by CCR investigators in the form of research proposals that are approved by the company. With the legalities attended to, the focus returns to the science.

Advancing Clinical Science

Linehan has devoted 27 years to studying the genetic basis of urologic cancers (see "A War on Kidney Cancer" in Vol. 1, No. 1 of *CCR connections*). He and his colleagues work with families of patients with rare mutations that lead to diseases like von Hippel-Lindau (VHL) and Birt-Hogg-Dube (BHD) syndromes. While treating these rare cases, the Linehan team also uses the knowledge it gains from studying these unique patient populations with known genetic predispositions to kidney cancer to develop better treatments for both familial and sporadic forms of the diseases. "We never promised the families that we would find the genetic basis for their disease," said Linehan. "So you can imagine the

CRADA History

Congress established CRADAs—Cooperative Research and Development Agreements—in 1986 as part of the Federal Technology Transfer Act to allow federal government laboratories to work with industry. However, it took several years to work out the details of implementation, and it has had varied degrees of success across government agencies. With approximately 100 active CRADAs at any one time, CCR accounts for approximately one-half of all CRADAs operating throughout the NIH.

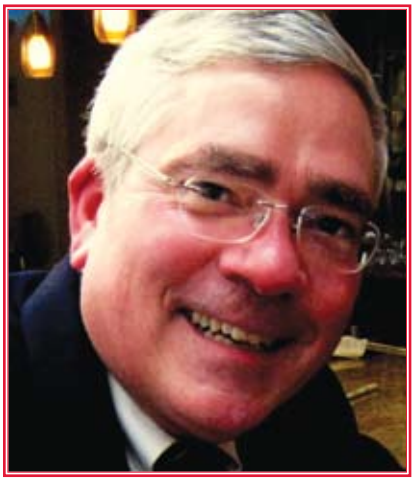
"The CRADA is the only mechanism by which the federal government can promise intellectual property rights to technology," explained Eric Hale, J.D., M.B.A. CRADAs allow companies the first option to license technology and rights that government researchers develop. CRADAs also allow the government to protect from disclosure proprietary information brought into the agreement and protect information emerging from the CRADA for an agreed-upon period. In return, companies can offer research funds and, more significantly, access to proprietary compounds and technologies.

thrill it was both for our research team and for the patients when we succeeded."

Linehan and his colleagues might have declared victory at that stage—how many researchers identify even one cancer-causing mutation in their lifetime? Instead, they turned their focus to the ultimate victory, searching for a curative treatment for kidney cancer.

They have now discovered four kidney cancer genes and developed unique cell lines from their patients that allow them to understand much more about the molecular pathways involved. Yet they still are not able to target many of the proteins in these pathways to develop treatment strategies. "We have found several good candidate molecules by working with the NCI Drug Screening Program in Frederick, which we are encouraged about," explained Linehan. "However, many other promising agents are owned by several different pharmaceutical companies. Having to negotiate individually with companies has really slowed us down."

Across the NIH campus, Mock has been working on elements of the same molecular pathways that Linehan finds affected in kidney cancers, but she approaches them from a different starting point. Mock's group has been studying the genetic predisposition of some mouse strains to the development of plasma cell tumors. "We have uncovered at least four genes that are involved in determining genetic susceptibilities," reported Mock. She and her postdoctoral fellow, Jyoti Patel, Ph.D., have only been working for about three years on pharmacological approaches to studying the pathways they have uncovered, but they immediately ran into difficulties obtaining the drugs that they needed. "In some cases, studying new agents in preclinical settings can be more difficult than doing so in actual clinical trials."



(Photo: Courtesy of G. Curt)

Gregory Curt, M.D.

The Umbrella CRADA:

A Genuine Win-Win Partnership Between NCI and Industry

- Eliminates duplicative research efforts
- Eliminates delays resulting from redundant legal review and approval
- Provides a forum for the exchange of ideas
- Allows for large-scale collaborations
- Allows for the development of multiple agents simultaneously
- Expedites the drug development processes

Both Mock and Linehan are enthusiastic about the Umbrella CRADA with AstraZeneca, which they emphasize has opened the lines of sharing and communication. The investigators meet with company scientists on a regular basis to share ideas and discuss projects. As Beverly Mock observed, "You're not only getting the drug, you're getting interaction with the company that has much preliminary data already gathered for the agent of interest…it's a great way for investigators to network and share protocols and ideas." As Linehan noted, "We have a lot of ideas and the companies also have a lot of great ideas and approaches, and when you get them together, it's magic."

Benefiting Drug Development

The Umbrella CRADA between CCR and AstraZeneca involves what Curt calls "one of our most exciting drugs" whose mechanism of action involves inhibition of mTOR, an important target in cancer research. The agreement covers a suite of drugs against this target and applies to any CCR laboratory or branch. As Curt put it, "We have not just one drug, but drugs and backup drugs. They have not just one branch but many branches. So why should you do a CRADA with the Urologic Oncology Branch only to find out that there's an interest in the Medical Oncology Branch for non-small cell lung cancer (NSCLC) and in the Radiology Oncology Branch for radiation sensitization?" Likewise, if one drug is dropped from development and replaced by another because of bioavailability or toxicity issues, the collaboration does not grind to a halt until a new CRADA can be established.

Like the investigators at CCR, the scientists at AstraZeneca appreciate the extent of the collaboration engendered by the Umbrella CRADA. "The science is shared—particularly, the preclinical science. Neither NCI nor AstraZeneca wants to waste resources by recapitulating the same thing within the company and institution."

Of course, great care must be taken any time a company releases a proprietary compound in drug development to an external organization for research. "We have an obligation as an entity developing a drug to be certain that the work being done with it makes sense," explained Curt. The Umbrella CRADA gives freedom to operate, but individual proposals are still subject to rigorous scientific review before AstraZeneca will agree to move forward. "There is always risk when you give up control of an experimental agent. So you mitigate that risk by working with people that you trust."

Curt sites numerous examples of standard CRADA agreements with NCI that have proven successful. "NCI has found important signals of activity in our drugs that will benefit patients that would have gone undiscovered." For instance, NCI scientists recently discovered that the off-target activity of AstraZeneca's drug Zactima™ is effective in treating medullary thyroid cancer in children. "Isn't it fantastic that one person's off-target effect is a potentially effective treatment for children with an aggressive although rare cancer?"

To learn more about CRADA and CCR's Office of Policy and Intellectual Property, please visit https://ccrod.cancer.gov/confluence/display/OPIPPub/Home.